# Clinical Investigation

# Duration of Type I Diabetes Affects Glucagon and Glucose Responses to Insulin-Induced Hypoglycemia

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*The glucagon response to hypoglycemia, which fulfills a primary role toward restoring the plasma glucose level, is blunted or absent in most patients with type I diabetes. To identify predictive factors for this abnormality and for the capability of glycemic counterregulation, we investigated the relationship between the duration of diabetes and glucagon and glucose responses to insulin-induced hypoglycemia. In 18 type I diabetic patients with 1 through 28 years of disease who had no detectable autonomic neuropathy, individual glucagon increments after insulin hypoglycemia were inversely correlated with the duration of disease ($r = -.53$, $P < .025$). Patients with disease for ten or fewer years showed a glucagon rise that was lower than in controls but significantly higher than in patients with a duration of more than ten years. The plasma glucose rise after the nadir correlated with peak glucagon increments ($r = .60$, $P < .01$); eight of the nine patients with glycemic increments comparable to normals had had diabetes for ten years or less. Thus, having diabetes for more than ten years implied that not only were glucagon responses to insulin hypoglycemia severely compromised but also that the abrupt restoration of plasma glucose levels was impaired. These findings should be taken into account when establishing goals and modalities for tight metabolic control.*

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The availability of new technology and growing evidence that sustained near-normoglycemia corrects in diabetic patients functional abnormalities that may represent prodromes of the classic complications[1-4] are encouraging the achievement of tight metabolic control of diabetes. Intensive insulin therapy has its complications, however, the most serious of which is the increased risk of profound hypoglycemia.[5] It would thus be valuable to isolate clinical characteristics capable of prospectively identifying patients at increased risk of this complication.

Under normal circumstances a decline in the plasma glucose level is briskly corrected by accelerated hepatic glycogenolysis driven by the increased secretion of epinephrine and glucagon.[6] Glucagon has been attributed a primary role in the recovery from hypoglycemia because, in the absence of its response, even exaggerated increments in epinephrine fail to restore plasma glucose to normal levels.[6,7]

Although patients with type I diabetes manifest, as a group, a blunted or absent glucagon response to hypoglycemia and compromised glycemic counterregulation,[7-10] individual patients may have adequate responses. The recent report by Bolli and co-workers[11] of a striking inverse correlation between the duration of type I diabetes and glucagon responses to hypoglycemia suggests that the duration of diabetes may be a useful clinical predictor of disturbances in glycemic counterregulation. In other studies, however, diabetic patients with clinical or experimental evidence of defective counterregulation could not be separated from those

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manifesting adequate responses on the basis of glucagon behavior nor of the duration of diabetes.[12,13]

We have thus sought to reexamine to what extent the duration of type I diabetes and attending glucagon responses to hypoglycemia can be useful in predicting the capability of restoring plasma glucose levels.

## Patients and Methods

Studies were approved by the Committee on Human Research of the University of California at San Francisco and an informed written consent was obtained from all participating persons. The clinical characteristics of the 18 patients with diabetes are summarized in Table 1. They were all ketosis-prone and insulin-dependent. At the time of study patients were, with the noted exception, all within ideal body weight, free from proliferative retinopathy, advanced kidney disease (serum creatinine levels were less than 1.3 mg per dl) and other vascular complications, none had resting tachycardia (more than 90 beats per minute) nor postural hypotension (a fall in systolic pressure of 30 mm of mercury or more). Control subjects were matched for age and sex and all were within ideal body weight. The only medication was insulin for the diabetic patients, all of whom were on twice-a-day injections of regular mixed with an intermediate-acting insulin preparation (NPH or Lente). Because we had elected to study patients under circumstances that would mimic their daily control, tests were done after an overnight admission to the General Clinical Research Center while the patients were receiving their usual insulin therapy. Insulin-tolerance tests were administered after an overnight fast, starting at 0800 hours, the diabetic patients having received their last insulin dose no later than 2000 hours the previous night. In all subjects an antecubital intravenous line was established and kept patent with an infusion of 0.9% saline solution and, after a 30-minute equilibration period, baseline blood specimens were obtained at 20- to 30-minute intervals. The insulin dose for diabetic patients was decided on the basis of three baseline glucose values: depending on actual levels and direction and rate of changes, we administered between 0.12 and 0.2 units per kg of body weight for fasting glucose levels of less than 150 mg per dl and between 0.2 and 0.5 units per kg for glucose levels greater than 150 mg per dl. Normal controls received 0.15 units per kg. To all subjects insulin was given as a bolus at zero time, with the exception of patients 2, 5, 6 and 9, who received the 0.4 to 0.5 units per kg dose. In these patients half of the insulin dose was given at zero time and half at 45 to 60 minutes, depending on the rate of decline of plasma glucose. Blood specimens were obtained every 15 minutes after the insulin injection; in six of the eight control subjects specimens were also obtained at 3, 6, 9 and 12 minutes after insulin injection to determine the extent of glucagon suppression.

In all specimens we measured plasma glucose,[14(p1)] pancreatic glucagon (antiserum 30K,[15] cortisol[16] and serum growth hormone levels.[17] Tests were considered valid for inclusion in the study when at least one plasma glucose value was below 40 mg per dl. The slope of the line connecting glucose values between zero time and the nadir was taken to describe the rate of glucose fall; on that, the half-life and the rate of disappearance (K) were calculated. Hormone increments were computed in individual subjects as the difference between the peak value after glucose nadir and the mean baseline value (−30 and 0 minutes); glucagon suppression was determined as the difference between the mean baseline value and the lowest level observed before the glucose nadir. The glycemic increment after hypoglycemia was computed in two ways: as the difference between the value recorded 15 minutes after the nadir and the nadir itself; and as the area under the curve described by the increments at 15 and 30 minutes postnadir, the value at the nadir having been assigned a value of zero.

Although no multisystemic testing for autonomic dysfunction was done, we had obtained in all patients a pulse rate in the basal state and during the performance of the insulin-tol-

TABLE 1.—*Clinical and Experimental Data on Patients With Diabetes*

| *Patient, Sex* | *Age Years* | *Duration of Diabetes Mellitus Years* | *Baseline Values* | | *Insulin Given units (per kg)* | *Plasma Glucagon Suppression pg/ml* | *Plasma Glucagon Increment in ITT pg/ml* |
|---|---|---|---|---|---|---|---|
| | | | *Glucose mg/dl* | *Glucagon pg/ml* | | | |
| 1* ♂ | 30 | 28 | 134 | 50 | 12.0 (0.15) | 27 | 33 |
| 2† ♂ | 27 | 22 | 156 | 140 | 30.0 (0.4) | 47 | 20 |
| 3 ♂ | 28 | 18 | 130 | 37 | 11.0 (0.15) | 19 | 20 |
| 4‡ ♀ | 20 | 17 | 111 | 33 | 12.0 (0.2) | 22 | 78 |
| 5 ♂ | 26 | 14 | 175 | 30 | 36.0 (0.4) | 13 | 23 |
| 6 ♀ | 42 | 14 | 288 | 145 | 34.0 (0.5) | 100 | 0 |
| 7 ♂ | 25 | 10 | 60 | 10 | 9.0 (0.15) | 0 | 70 |
| 8 ♂ | 25 | 10 | 109 | 88 | 15.0 (0.2) | 31 | 102 |
| 9 ♂ | 22 | 8 | 250 | 57 | 38.0 (0.5) | 27 | 110 |
| 10 ♂ | 20 | 8 | 89 | 70 | 10.0 (0.15) | 0 | 108 |
| 11 ♂ | 27 | 7 | 185 | 44 | 25.0 (0.3) | 84 | 90 |
| 12 ♂ | 25 | 5 | 104 | 22 | 10.0 (0.15) | 16 | 39 |
| 13 ♂ | 28 | 5 | 229 | 77 | 21.0 (0.25) | 60 | 189 |
| 14 ♂ | 19 | 4 | 88 | 56 | 9.6 (0.15) | 8 | 55 |
| 15 ♂ | 23 | 4 | 73 | 11 | 8.2 (0.12) | 12 | 36 |
| 16 ♂ | 28 | 2 | 120 | 110 | 9.0 (0.15) | 32 | 300 |
| 17 ♂ | 20 | 2 | 167 | 118 | 18.0 (0.24) | 27 | 90 |
| 18 ♂ | 18 | 1 | 132 | 97 | 15.0 (0.2) | 64 | 103 |

ITT = insulin tolerance test

*Patient also has impotence.

†Sensory neuropathy and 2+ proteinuria are also present.

‡The patient weighs 20% more than ideal body weight.

erance test, as well as supine and standing blood pressures. In patients 2, 3 and 6, who showed the least of all glucagon responses to hypoglycemia, we did a Valsalva's maneuver, a reliable and reproducible test of autonomic nerve function.[18] The results are expressed as the "Valsalva ratio," which is the longest RR interval after the maneuver (reflecting the overshoot bradycardia) to the shortest interval during the maneuver (reflecting the tachycardia during strain).

Group data are expressed as the mean ± standard deviation. The two groups were compared using the Student's *t* test (nonpaired analysis). When more than two groups were compared, statistical analysis was done by analysis of variance, followed by multiple-range testing (Duncan's). Least-squares regression was used for line fitting.

## Results

### *Glucagon Response to Insulin-Induced Hypoglycemia and Duration of Diabetes*

In normal subjects plasma glucose nadirs (28 ± 5 mg per dl) occurred between 15 and 30 minutes after the injection of insulin and the peak glucagon increment (184 ± 71 pg per ml) was noted between 30 and 45 minutes. In diabetic patients plasma glucose nadirs (30 ± 9 mg per dl) were reached between 30 and 120 minutes after giving insulin, depending on the initial plasma glucose values (reported in Table 1). The basal plasma glucagon level (66 ± 42 pg per ml) was not different from that of normal subjects (66 ± 40), but a wide spectrum of responses to hypoglycemia was observed: as shown in Table 1, increments ranged from 300 pg per ml to undetectable. A significant inverse correlation was found (Figure 1) between duration of diabetes and glucagon responses to hypoglycemia ($r = -.53, P < .025$).

Because no normal glucagon responses were noted in patients with diabetes for more than ten years, we compared their glucagon increments with those in controls and in patients who had had diabetes for ten years or less (Table 2). The group of patients who had had diabetes for more than ten years had a glucagon rise of 29 ± 26 pg per ml, significantly lower than that of controls ($P < .005$) and patients with 10 or fewer years of disease ($P < .025$). The difference with the latter group occurred despite the fact that none of the experimental variables that may have positively or negatively affected the glucagon response (basal glucose, glucose nadir, absolute glucose decline, insulin administered, rate of glucose decline, glucagon suppression) were significantly different between the two groups.

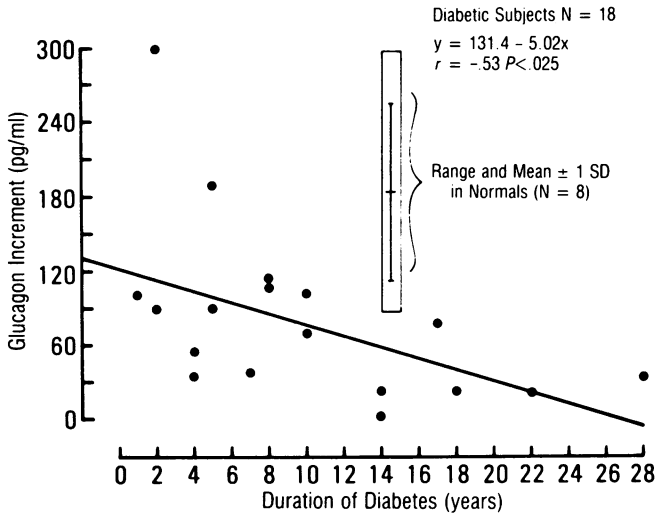


**Figure 1.**—Correlation between duration of type I diabetes and peak increments of plasma glucagon level after insulin hypoglycemia. SD = standard deviation.

Patients with ten or fewer years of diabetes also showed, as a group, a lesser glucagon response to hypoglycemia than controls (107 ± 71 pg per ml versus 184 ± 71 in controls, $P < .05$). The only other variable that differed statistically between the two groups was the rate of glucose fall (3.6 ± 1.6 mg per dl a minute versus 5.2 ± 1.7 in controls, $P < .05$). Of interest, however, is that no significant correlation was found between the individual rate of glucose disappearance and glucagon increment after hypoglycemia in either group. In addition, in diabetic patients there was no correlation between basal glucose levels, insulin administered, glucagon suppression and glucagon increments after hypoglycemia.

### *Glucagon Responses to Hypoglycemia and Restoration of Plasma Glucose*

In normal subjects, 15 minutes after the observed nadir, plasma glucose levels had increased by 15 ± 6 mg per dl and the range of increments was 5 to 27 mg per dl. Among the 12 patients with ten or fewer years of disease, a glycemic response within the range of normal was displayed by 8 (66%), whereas among the 6 patients with diabetes for a longer duration, the glycemic response of only 1 (16%) fell within the control range. Overall, a positive correlation was evident (Figure 2) between increments in glucagon and in-

TABLE 2.—*Comparison of Group Data for Metabolic Variables and Glucagon Responses to Hypoglycemia*

| | *Normal Subjects N = 8 Mean ± SD* | *Patients With ≤ 10 Years of DM N = 12 Mean ± SD* | *Patients With > 10 Years of DM N = 6 Mean ± SD* |
|---|---|---|---|
| Basal glucose, mg/dl | 86 ± 8 | 133 ± 61 | 165 ± 63* |
| **Insulin given, units/kg** | 0.15 ± 0.00 | 0.21 ± 0.10 | 0.3 ± 0.15 |
| Plasma glucose nadir, mg/dl | 28 ± 5 | 30 ± 9 | 30 ± 9 |
| **Absolute plasma glucose decline, mg/dl** | 57 ± 9 | 101 ± 53 | 131 ± 66* |
| Rate of plasma glucose decline (K), mg/dl/min | 5.2 ± 1.7 | 3.6 ± 1.6* | 3.0 ± 0.6* |
| **Plasma glucagon suppression, pg/ml** | 13 ± 11 | 30 ± 26 | 38 ± 32 |
| Plasma glucagon increment, pg/ml | 184 ± 71 | 107 ± 71* | 29 ± 26†‡ |

DM = diabetes mellitus, SD = standard deviation

*$P < .05$ versus controls. †$P < .005$ versus controls. ‡$P < .025$ versus DM ≤ 10 years.

crements in plasma glucose 15 minutes postnadir ($r = .60$, $P < .01$). Similar results were obtained when the correlation was sought between the increments in glucagon and the areas under the curve for the plasma glucose rise during the 30 minutes following the nadir ($r = .56$, $P < .025$). No correlation was found between glycemic rise and basal glucose ($r = .18$) or administered dose of insulin ($r = -.29$). When we examined whether a relationship existed between the duration of diabetes per se and glycemic restoration after hypoglycemia (15-minute increments in plasma glucose level or a 30-minute area under the curve), we found only a poor correlation ($r = -.377$), which did not achieve statistical significance.

*Cardiovascular Variables*

The mean resting pulse rate did not differ between the eight patients with glucagon increments within the normal range (64 ± 6 beats per minute) and patients with blunted glucagon rises (68 ± 9). When, however, resting pulse rates were compared between patients who had had diabetes for ten years or less and those who had had the disease for a longer duration, a significant difference was noted: 62 ± 5 beats per minute versus 73 ± 7, $P < .005$. Pulse rate increments during hypoglycemia did not differ in the two groups: 28 ± 10 beats per minute in the shorter duration patients versus 24 ± 6. No patients had on standing a drop in systolic blood pressure of more than 10 mm of mercury. The Valsalva ratio was 1.56 in patient 2, 1.4 in patient 3 and 1.3 in patient 6, values of 1.21 or greater being considered normal.[18]

*Growth Hormone and Cortisol Responses to Hypoglycemia*

The basal serum growth hormone level was 4.2 ± 2.4 ng per ml in normal subjects and 4.2 ± 2.2 in patients with diabetes. The respective increments after hypoglycemia were 44 ± 18 versus 39 ± 24 (not significant). The basal plasma cortisol level was 16 ± 4.7 μg per dl in controls and 16 ± 5.2 in patients with respective increments after hypoglycemia of 21 ± 7 versus 16 ± 9 (not significant).

## Discussion

During this investigation on counterregulatory events in patients with type I diabetes for various durations, three observations were made: (1) an increasing duration of diabetes is accompanied by a progressive blunting of the glucagon response to insulin-induced hypoglycemia, (2) factors other than the duration of diabetes per se must contribute to the subnormal rises because these are occasionally noted in patients with only a few years of disease and (3) the capability to restore plasma glucose levels is significantly correlated with the capability to mount a glucagon response to hypoglycemia and both are severely compromised in patients with diabetes for more than ten years.

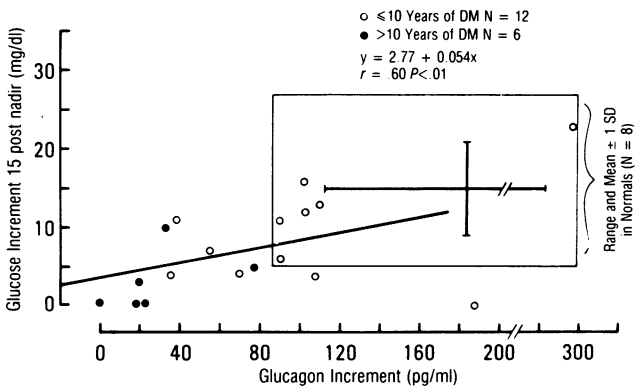


**Figure 2.**—Correlation between plasma glucagon response and glucose increments after hypoglycemic nadir in patients with type I diabetes mellitus (DM). The rectangle encompasses the range of responses in normal control (glucagon along the abscissa, glucose along the ordinate). SD = standard deviation.

Several considerations militate against the possibility that the progressively blunted or absent glucagon response to hypoglycemia might be accounted for by experimental variables. Basal glycemic levels are unlikely to be of relevance since the same blunted or absent glucagon responses to hypoglycemia have been found in diabetic patients studied after overnight return to normal of the plasma glucose level[11] or long-term improvement of metabolic status.[7] Furthermore, inducing hyperglycemia before the insulin tolerance test in normal subjects may delay, but does not impair, the glucagon response to hypoglycemia.[8,19] And this is despite the additional facts that to achieve hypoglycemia after inducing hyperglycemia, larger and multiple doses of insulin are required, glucagon levels become transiently suppressed and plasma glucose levels fall at a slower rate.[18] In agreement with the above observations in normal persons are the present findings in diabetic patients of absent correlations between metabolic variables and glucagon increments after hypoglycemia. Moreover, the glucagon response to hypoglycemia in patients with diabetes for more than ten years was significantly lower than in patients with the disease for a shorter duration, despite the fact that concurrent metabolic variables did not show a statistical difference.

The decreased glucagon response to hypoglycemia with increasing duration of type I diabetes could be regarded as a "complication" whose cause and pathogenesis are, however, not clearly defined. Loss of α-cell secretory capacity cannot be implicated since the same patients who are "nonresponders" to insulin hypoglycemia instead manifest glucagon hyperresponsiveness to other stimuli; autonomic neuropathy might exacerbate the defect[10] but is by no means a necessary determinant. In fact, in the absence of any sign of vagal and sympathetic neuropathy, many diabetic patients do not have a normal glucagon response to hypoglycemia.[7,10] Among our patients nonresponders did not show resting tachycardia or abnormal responses to Valsalva's maneuvers—accepted indices of parasympathetic dysfunction[18]—and no one suffered from sufficient loss of sympathetic function to cause postural hypotension. It has been observed that patients with the best preserved glucagon response to hypoglycemia have the most residual β-cell function.[20,21] Insulin secretory reserve has been shown to deteriorate with an increasing duration of diabetes[22] and the temporal pattern parallels quite closely the time course of deterioration of glucagon response to hypoglycemia observed in our study. Although the mechanism of a causal relationship, if any, between the two phenomena remains at this time speculative, it could be hypothesized that disappearance of the prevailing type of islet cells (β-cells) or the very processes leading to such disappearance[23] may, for architectural or direct pathogenetic reasons, disturb neighboring cells or local integrating systems important for

normal responses to hypoglycemia. In such a case, the compromised glucagon response to hypoglycemia would be a complication of the pathogenesis of type I diabetes rather than of long-term metabolic derangement and even tight glycemic control since the onset of diabetes might not succeed in fully preventing the abnormality. Only prospective studies in patients under meticulous control will help isolate structural from metabolic causes.

The important contribution of glucagon to brisk counterregulation was confirmed in our patients by the correlation found between glucagon responses to hypoglycemia and plasma glucose increments. However, glucagon response was not the only determinant toward restoration of plasma glucose. Two patients with substantial glucagon increments did not have an appropriate increase in their plasma glucose levels; they may belong to the category of patients who have delayed disappearance of insulin caused by insulin antibodies.[11] In the few patients whose plasma glucose level rapidly rose despite subnormal glucagon responses, this most likely occurred through an augmented compensatory epinephrine discharge.[24,25] Such multifactorial contributions to glucose counterregulation probably account for the fact that the correlation between glucagon and glucose responses was not absolute and that we could not identify a significant correlation between the duration of diabetes per se and the magnitude of the glycemic response. The fact, however, that eight of the nine patients showing a brisk glycemic increment had diabetes for fewer than ten years may be taken as a warning that beyond this duration of diabetes the crucial safety mechanisms—which do not include growth hormone and cortisol—become generally less efficient. This is in agreement with the finding by White and associates,[13] whose patients with inadequate counterregulation had no responses of either glucagon or epinephrine after a duration of diabetes of $15.9 \pm 2.8$ years (mean $\pm$ standard error of the mean).

At least two clinical implications can be drawn from these studies. The first is that because the glucagon response to hypoglycemia may be lost quite early, the effectiveness of the epinephrine response should be safeguarded. In particular, since the contribution of epinephrine to counterregulation is mediated through $\beta$-adrenergic receptors,[25,26] $\beta$-adrenergic blockers should be used with caution. The second clinical implication is that because the capability for counterregulation tends to decline with a progressive duration of diabetes, targets and modalities of treatment need to be periodically reassessed, possibly in a preventive fashion. These considerations should by no means halt attempts at ameliorating the metabolic status of diabetic patients; among other benefits, good diabetic control may result in improved glucose recovery from hypoglycemia, possibly by increasing the activity of liver enzymes involved in glycogenolysis and gluconeogenesis.[27] Special caution should, however, be exercised in the approach to patients with long-standing disease.

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